# A Novel Technique for the Preparation of Secondary Fatty Amides

**A technique for the synthesis of monosubstituted fatty amides at low temperature and ambient pressure was developed. This method involved the condensation of an amine with a triacylglycerol. The primary amine (ethyl, *n*-butyl, *n*-hexyl and *n*-octyl were tested) acted as reagent and solvent for the fatty substrates. No additional organic solvent or catalyst was added. Tallow, vegetable oils and fish oil all served well as substrates, as did pure tripalmitin. The rate of amidation was dependent upon temperature and the ratio of fat to amine. In a series of experiments conducted with tallow and *n*-butylamine at a fat:amine molar ratio of 1:16, amidation could be carried out at 20°C, producing *n*-butyltallowamide in 83% yield in 24 hr. When the fat:amine molar ratio was reduced to 1:8, and the temperature raised to 45°C, the amide yield was 87.6% in 24 hr. When the reaction was carried out at the boiling point of *n*-butylamine (78°C) and at a fat: amine ratio of 1:8, the amide yield was 93.2% in 4 hr. The reaction progressed more rapidly with higher molecular weight amines. The identity and purity of the amides was assessed by thin-layer chromatography and confirmed by elemental analyses and infrared and $C^{13}$ nuclear magnetic resonance spectroscopy.**

KEY WORDS: Amidation, amide, cod liver oil, corn oil, cottonseed oil, ethylamine, *n*-butylamine, *n*-butyl-hexadecanamide, *n*-hexylamine, *n*-octylamine, soybean oil, tallow, triacylglycerol, tripalmitin.

Fatty amides are compounds that exhibit low reactivity and high thermal stability. Their chemical properties vary depending on the length of the hydrocarbon chain and the nature of the substituent on the nitrogen atom. Fatty amides have many different applications (1). These include anti-slip and anti-block additives for polyethylene films, water repellants for textiles, coatings for paper, mold-release agents, lubricant additives, printing ink additives, defoaming agents and flow improvers. The production of fatty amides has increased significantly each year, due to the discovery of new uses and the expansion of existing applications. In 1988, 286 million pounds of fatty amides were produced in the U.S. (2). In industry, the monosubstituted amides (RCONHR') are typically produced from purified fatty acids and primary amines at temperatures of 140–170°C under moderate pressure (3). There are alternative methods for producing fatty amides. In the Schotten-Baumann reaction (4,5), a fatty acylchloride is reacted with an amine. Jordan and Port, using sodium methoxide as catalyst, reported a 96% conversion of *n*-butylamine and methyl stearate to *n*-butylstearamide (6). However, both of these methods involve the use of hazardous materials.

We report here an alternate method of fatty amide synthesis, which consumes less energy than methods currently employed and uses triacylglycerols as reactants rather than fatty acids. This study included a synthetic monoacid triacylglycerol and natural triacylglycerols from animal fats, vegetable oils and fish oils, as well as a wide range of amines. Conditions, such as temperature, time, unsaturation of the fatty substrate and molar ratios of the reactants, were investigated. The chemical literature (1,3,7,8) was searched to identify prior descriptions of low-temperature fatty amide preparation. No report of amidation under mild conditions with relatively nonhazardous reagents was found.

## EXPERIMENTAL PROCEDURES

*Materials.* The primary amines (ethyl, *n*-butyl, *n*-hexyl, *n*-octyl) and palmitoyl chloride were purchased from Aldrich Chemical Co. (Milwaukee, WI). The suppliers of the fats and oils were: bleached tallow, Chemol Inc. (Greensboro, NC); cottonseed oil, Sigma Chemical Co. (St. Louis, MO); soybean oil, NPB Marketing, Inc. (Memphis, TN); corn oil, Best Foods, CPC International, Inc. (Englewood Cliffs, NJ); cod liver oil, E. R. Squibb & Sons, Inc. (Princeton, NJ); tripalmitin, Eastman Kodak Co. (Rochester, NY). All reagents were used as received. Silica Gel G Plates (2.5 × 20 cm, 250 μm and 500 μm) were purchased from Analtech, Inc. (Newark, DE). High purity solvents were supplied by Baxter Health Care Corp., Burdick and Jackson Div. (Muskegon, MI). Sigma Chemical Co. supplied the thin-layer chromatography (TLC) standards.

*Reference amide synthesis by the acid chloride route.* Standard *n*-butylpalmitamide was prepared by the following procedure (9). *n*-Butylamine (10.6 g, 0.14 mole) was dissolved in 100 mL methylene chloride, containing 10 mL pyridine and chilled to 10°C. Palmitoyl chloride (40.4 g, 0.15 mole) was added dropwise to the amine solution over a 5-min period and stirred for 1 hr. Excess pyridine was neutralized with 4N hydrochloric acid, and the organic layer was washed with distilled water until neutral. The organic phase was passed through a Florisil (Floridin Co., Berkley Springs, WV) column to remove impurities. Residual amounts of free fatty acid were removed by titrating an alcoholic amide solution with 0.1 N NaOH. The product was crystallized from methylene chloride at 0°C. *n*-Butylpalmitamide (30.2 g, m.p. 72.0–72.5°C, Lit. 72°C) (10) was obtained in 66.3% yield. Infrared (IR): NH absorption at 3300 $cm^{-1}$, amide absorption at 1638 $cm^{-1}$ and 1548 $cm^{-1}$. Analysis calculated for $C_{20}H_{41}NO$: C, 77.08%; H, 13.29%; N, 4.50%; found C, 76.99%; H, 13.12%; N, 4.42%. $C^{13}$NMR, ($CDCl_3$) δ, **relative integration area:** 13.6, 1 ($\underline{C}H_3$); 14.0, 1 ($\underline{C}H_3$), 20.0, 1 ($\underline{C}H_2$); 22.6, 1 ($\underline{C}H_2$); 25.8, 1 ($\underline{C}H_2$); 29.3-29.6; **10** ($\underline{C}H_2$); 31.8, 2 ($\underline{C}H_2$); 36.9, 1 ($\underline{C}H_2CONH$); 39.2, 1 ($CONH\underline{C}H_2$); 172.9, 1 ($\underline{C}ONH$).

*Amide preparation from tripalmitin.* Tripalmitin (10 mmol) and *n*-butylamine (80 mmol) were placed in a 25-mL Erlenmeyer flask, which was sealed and shaken at 150 rpm at 45°C for 24 hr in an orbital shaker. *n*-Butylpalmitamide (7.2 g, m.p. 72–72.5°C) was obtained in 80% yield. As this reaction proceeded, the solution became solid, preventing the amidation from going to completion. To overcome this condition, the experiment was repeated at 60°C for 8 hr. At this temperature, the reaction mixture remained fluid throughout the incubation and

*n*-butylpalmitamide (8.2 g, m.p. 72–72.5°C) was obtained in 91% yield. Analysis calculated for $C_{20}$ $H_{41}$ NO: C, 77.08%; H, 13.29%; N, 4.50%. Found: C, 76.41%; H, 12.65%; and N, 4.42%. The $C^{13}$ nuclear magnetic resonance (NMR) spectrum was indistinguishable from that obtained from *n*-butylpalmitamide synthesized by the acid chloride route.

*Amide preparation from fats and oils.* The procedure used for tallow is typical. For low-temperature (20°C and 45°C) incubations, tallow (10 mmol) and *n*-butylamine (80 mmol) were incubated as described above for tripalmitin. Samples were removed periodically for analysis. The extent of amidation was monitored by TLC. High-temperature amidation of tallow was performed as follows. Tallow (28 mmol) and *n*-butylamine (224 mmol) were placed in a 250-mL round-bottom flask equipped with a reflux condenser. The flask was heated on a steam bath. Samples were removed hourly over a 4-hr period for TLC analyses. Afterwards, the reaction material was dissolved in 100 mL hexane and washed with 10 mL distilled water three times to remove glycerol and excess *n*-butylamine. *n*-Butyltallowamide was crystallized from hexane at 0°C to obtain a white powder.

*Analysis by TLC.* The method of Bilyk *et al.* (11) was employed with silica gel G plates that had been prewashed in a tank of methanol for 5 min. The plates were spotted with 10 μL of a 2% (w/v) concentration of sample in chloroform. Identification was made by comparison with known standards.

Amide yield was determined by preparative TLC on 500-μm thick silica gel plates. A weighed sample was dissolved in ethyl acetate-methanol (80:20, v/v) and applied to the plate by means of a streaker (Applied Science Laboratories, Inc., State College, PA). The plates were then developed as previously described (11). Upon drying, the plate was sprayed with a 0.1% ethanolic solution of 2,7-dichlorofluorescein, which permitted detection of the amide band under ultraviolet (UV) radiation. The band was scraped from the plate and extracted with warm ethyl acetate-methanol (80:20, v/v) into preweighed vials. Solvent was removed with a nitrogen stream, and the vials were reweighed to determine amide weight. All analyses were run in duplicate and averages are reported.

## RESULTS AND DISCUSSION

After determining that mono-substituted fatty amides could be prepared from tallow and *n*-butylamine under mild conditions (45°C and atmospheric pressure), studies were conducted to determine the optimal amount of *n*-butylamine required at 45°C. At a tallow:amine molar ratio of 1:3, the reaction mixture solidified during incubation, and the reaction did not proceed to completion. The amount of amine was increased by increments. A final tallow:amine molar ratio of 1:8 resulted in full solubility of the reactants and products over a 24-hr period at 45°C. When the amount of amine was further increased to a molar ratio of 1:16, the reaction mixture remained fluid even at room temperature. These observations demonstrate that the amine serves as a solvent as well as a reactant. TLC analyses of the amidation of tallow by *n*-butylamine at three different temperatures and two different tallow:amine molar ratios are found in Figure 1. At shorter reaction times, di- and monoglyceride intermediates were evident. Eventually all the diglycerides disappeared, but small amounts of monoglyceride were still present after the longest incubation times tested. The compositions of these mixtures were determined by preparative TLC and are listed in Table 1. As expected, the rate of amidation increased with temperature. The best yield (93.2%) was

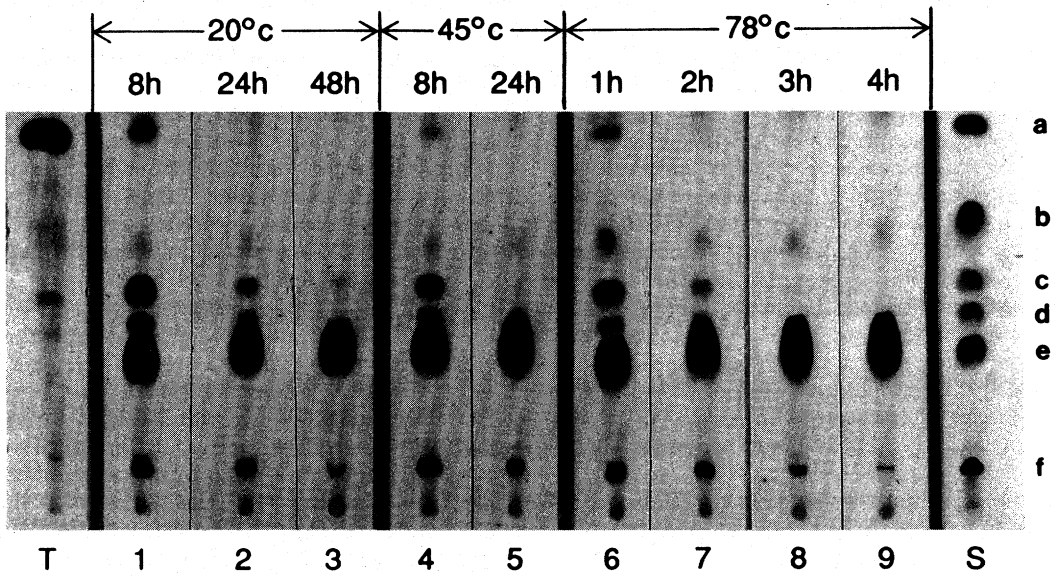


**FIG. 1. Effect of temperature on the amidation of tallow with *n*-butylamine. Lane T, unreacted tallow. Lanes 1, 2, and 3, reaction times: 8, 24 and 48 hr at 20°C and tallow:*n*-butylamine molar ratio (1:16). Lanes 4 and 5, reaction times: 8 and 24 hr at 45°C; tallow:*n*-butylamine molar ratio (1:8). Lanes 6, 7, 8, and 9, reaction times: 1, 2, 3 and 4 hr at 78°C; tallow:*n*-butylamine molar ratio (1:8). Lane S, standard mixture: a, triglyceride; b, fatty acid; c, 1,3 diglyceride; d, 1,2 diglyceride; e, *n*-butylpalmitamide; f, monoglyceride.**

TABLE 1

**Effect of Reaction Conditions on the Production of *n*-Butyltallowamide**

| Figure 1 lane | Temperature (°C) | Time (hr) | Molar ratio: tallow to amine | Percent[a] | | |
|---|---|---|---|---|---|---|
| | | | | Amide | Triglyceride | Mono- and diglycerides |
| 1 | 20 | 8 | 1:16 | 71.7 | 6.2 | 22.1 |
| 2 | 20 | 24 | 1:16 | 83.0 | — | 17.0 |
| 3 | 20 | 48 | 1:16 | 86.0 | — | 14.0 |
| 4 | 45 | 8 | 1:8 | 81.0 | 4.0 | 15.0 |
| 5 | 45 | 24 | 1:8 | 87.6 | — | 12.4 |
| 6 | 78 | 1 | 1:8 | 76.5 | 3.8 | 19.7 |
| 7 | 78 | 2 | 1:8 | 78.9 | — | 21.1 |
| 8 | 78 | 3 | 1:8 | 86.6 | — | 13.4 |
| 9 | 78 | 4 | 1:8 | 93.2 | — | 6.8 |

[a]Determined from the weight of the sample recovered after preparative TLC.

obtained at 78°C in 4 hr. The product from the 4-hr reaction at 78°C was isolated and crystallized as a white powder, *n*-butyltallowamide, 18.9 g (70.2% yield), m.p. 53–57°C; IR: NH absorption at 3299 $cm^{-1}$, amide absorption at 1638 $cm^{-1}$ and 1548 $cm^{-1}$.

To establish that the method described here achieves the amidation of the fatty acids of triglycerides, tripalmitin and *n*-butylamine were incubated as described in Experimental Procedures and the resulting material was recovered for characterization. Elemental analysis, IR spectra, and NMR spectra of the product were identical to those obtained from *n*-butylpalmitamide synthesized by the standard acid chloride route as described in Experimental Procedures.

The suitability of ethyl *n*-butyl, *n*-hexyl and *n*-octyl primary amines for the amidation of tallow was investigated at 45°C (Fig. 2). A tallow:amine molar ratio of 1:8 was used. Samples were fractionated by the TLC method described above. Analysis of material recovered from the amide region of the TLC plate confirmed the presence of tallowamide. As can be seen in Figure 2, the order of amine reactivity is ethylamine <*n*-butylamine <*n*-hexylamine <*n*-octylamine, demonstrating that amidation is accelerated as the amine becomes more lipophilic. The acceleration is such that for *n*-octylamine, the largest amine examined, amidation is essentially complete after 4-hr incubation.

The amidation procedure was tested on tallow, cottonseed oil, soybean oil, corn oil and cod-liver oil (data not shown). In each case, a 1:8 molar ratio of oil to *n*-butylamine was used. Samples were removed after 4, 8 and 24 hr of incubation at 45°C and analyzed by TLC. Although the degree of unsaturation of the oils varied widely, as indicated by their iodine values (tallow, 49.5; cottonseed, 105.7; soybean 130.0; corn 122.6; cod-liver 165) (12), the oils reacted at approximately the same rate, and amidation was nearly complete at 24 hr. This observation demonstrates that distal double bonds do not participate in amidation.

The amidation method described here offers several advantages over existing reaction schemes in that only relatively low temperatures and ambient pressure are needed. In addition to reducing energy requirements, these conditions minimize the occurrence of off-colors and

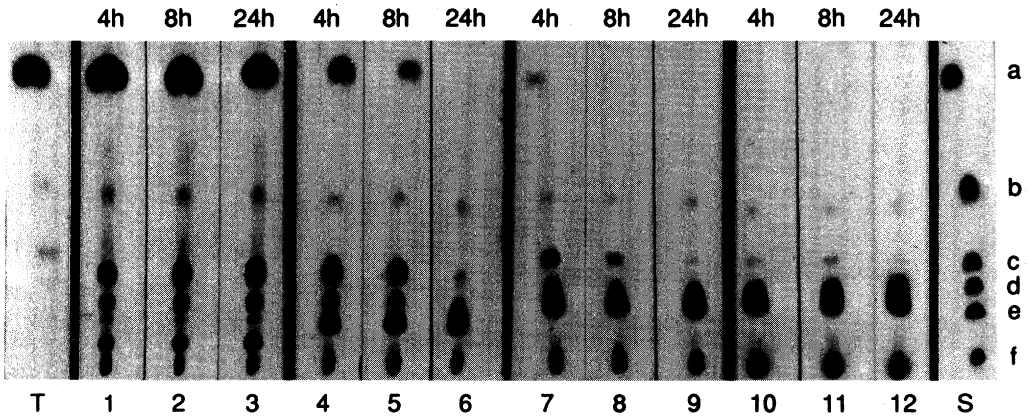


**FIG. 2. Amidation of tallow with primary amines at 4, 8 and 24 hr at 45°C. Lane T, unreacted tallow. Lanes 1, 2, and 3, tallow:ethylamine molar ratio (1:8). Lanes 4, 5, and 6, tallow:*n*-butylamine molar ratio (1:8). Lanes 7, 8, and 9, tallow:*n*-hexylamine molar ratio (1:8). Lanes 10, 11, and 12, tallow:*n*-octylamine molar ratio (1:8). Lane S, standard mixture (see Fig. 1).**

degradation products in the resulting amides. Such reactions can be significant with current amidation protocols. Reaction mixtures for the method described here are simple in composition, requiring neither additional solvent nor catalyst. The triglycerides themselves serve as reactants, with no need for their prior hydrolysis or conversion of their fatty acids to methyl esters. A wide range of triglycerides and amines serve as reactants, and the production of amides is essentially quantitative.


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